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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/535,588

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Tejal Ashwin Desai

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GREENLEE WINNER AND SULLIVAN P C

4875 PEARL EAST CIRCLE

SUITE 200

BOULDER, CO 80301

EXAMINER

KOSAR, AARON J

ART UNIT

PAPER NUMBER

1651

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/535,588	Applicant(s) DESAI ET AL.	
	Examiner AARON J. KOSAR	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17, 20 and 26-29 is/are pending in the application.
- 4a) Of the above claim(s) 8-17, 20 and 26-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's amendment and argument filed February 26, 20008 in response to the non-final rejection, are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Applicant has amended the claims by introducing new claim 29. Claims 1-17, 20 and 26-29 are pending. Claims 8-17, 20, and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 1-7 and 29 are pending and have been examined on the merits.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 and 29 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims presently recite limitations that do not require any manipulation and/or isolation; and, thus, may broadly and reasonably be interpreted as being drawn to products of nature.

Response to Arguments

Applicant has argued that the amended description of the composition requires artificial manipulations. Applicant's arguments have been fully considered but found to be not persuasive. In response to applicant's arguments and amendments, it is noted that the composition is still broadly and reasonably interpreted as being drawn to products of nature since the components

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and the cooperative arrangements thereof are consistent with tissues/organs, for example, vascular tissue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by (i)

FAWCETT (Bloom and Fawcett, “Blood, Lymph, and Vascular Systems” A Textbook of Histology, 12th Ed., 1994, pages 368-381.) or (ii) ISHIBASHI (Ishibashi, K. and Yamamoto, F. “Macromolecular assemblies in hybrid vascular graft reconstructed with three cell types” Akita Igaku. 2002, 29(2), pages 123-134 (CAS ABSTRACT) *and* as evidenced by PAULEV (Paulev, P.-E. "Systemic Resistance and Hypertension" Textbook in Medical Physiology And Pathophysiology Essentials and clinical problems. Copenhagen Medical Publishers, 2000, chapter 9, 16 pages.)

The claims are in general drawn to a plurality of layers, wherein the layers are vertically stacked and have a vertical thickness of less than one millimeter.

FAWCETT teaches mammalian blood vessels, comprising multiple layers vertically stacked (e.g page 370, figure 12-3). Fawcett teaches that the basic arterial organization comprises a distribution of cells within: (1) *tunica intima*, comprising squamous endothelial cells, (2) *tunica media*, comprising primarily (not exclusively) smooth muscle cells, and (3) *tunica adventitia*, comprising fibroblasts (page 368, ¶4; page 270, ¶2 (*intima*); page 271, ¶2 (*media*); page 372, ¶1 (*adventitia*)). The primary cell populations of the tissue layers are not exclusive and may

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comprise other cells/tissues/extracellular components (e.g figure 12-3, page 370 (veins); figure 12-10, page 376 (axons)). The cells, extracellular matrix, collagen fibers, etc. provide support for each other and each layer and are optically transparent, though enhanced by staining (e.g. figure 12-2-A/B, page 369). Blood vessels may be of various dimensions, though, measuring from the lumen, the layers may be vertically measured on the order of the micrometer scale (e.g. figure 12-14, page 380, scale bar is 25 μm .).

ISHIBASHI anticipates the claims by teaching a three-layered graft comprising sequentially endothelial cells (EC), vascular smooth muscle (VSM), and fibroblasts (FC) entrapped in collagen type I mixed gel (e.g. abstract).

To the extent that Fawcett or Ishibashi are silent with respect to measuring of shear forces, the shear force exerted by blood flow (e.g. 120mmHg systole; “coronary bloodflow is maintained at 200-250 ml min⁻¹.”, see PAULEV page 2, §1.1) would inherently provide the surface of the graft with at least a degree of shear force resistance to the extent claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over GRIFFITH (US 6,197,575 B1).

The claims are generally drawn to a multilayer microculture comprising (a) a plurality of vertical layers, (b) at least one cell type per layer, (c) a biopolymer, and (d) a 1 mm vertical dimension.

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The dependent claims are further drawn to the intrinsic properties of the composition and the identity of the cell(s) and a support material.

GRIFFITH teaches a multilayer microculture comprising three dimensional networks; cells of one or more type, including endothelial and/or hepatocyte cells; and, a dimension of 75-1000 μm and volume comprising $1\text{cm}^2 \times 1\text{mm}$ (column 6, ¶2). Griffith also teaches “microtissues are layered together to form microscale tissue or micro-organ arrays.. and consist of tissues stacked on top of each other, side-by-side each other, or both..[and] may be interconnected or isolated”(column 6, ¶3; see also column 25, ¶ 2 “staged delivery”). Additionally Griffith teaches a variety of cells (e.g. nerve cells, etc.: column 19, last ¶ and portion spanning column 20) and the attachment of cells to polystyrene Petri dishes coated with collagen (type I)(column 39).

To the extent that Griffith is silent regarding the explicit combinations of the instant invention and claims, it would have been obvious to combine the elements to produce a multi-layered microculture as claimed, because Griffith teaches that a variety of methods may be used to create micromatrices including three-dimensional printing and that a variety of cells may be used (including cells which intrinsically secrete extracellular matrix (ECM) proteins).

Griffith is relied upon for the reasons discussed above. If not expressly taught by Griffith, based upon the overall beneficial teaching provided by this reference with respect optimal dimensions (column 3, ¶1) in the manner disclosed therein, the adjustments of particular conventional working conditions (e.g., determining one or more suitable dimensions in which to produce such a product), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

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From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant has argued that Griffin does not teach polymerized biopolymers and matrix thereof comprising cells distributed within said matrix. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., dispersion by the method outlined in the specification, page 5, ¶1, (a)-(f)) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus where Griffith's teaches for example "cells seeded into channels of biodegradable polymer scaffolds" (column 39, Example 3), this is broadly and reasonably interpreted to constructively teach dispersing cells into multiple channels throughout the biopolymer matrix. Polymerization is inherent to the chemical structure of a biopolymer.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the

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forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. For the reasons of record and those presented above, the ground of rejection are maintained.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. NAUGHTON (US 5,032,508, US 5,160,490) *teaches a three-dimensional cell and tissue culture system, considered relevant in teaching the general state of the art with respect to multilayer cell cultures.*

TAN (Tan, W. et al. "Evaluation of Nanostructured Composite Collagen-Chitosan Matrices for Tissue Engineering" Tissue Engineering. 2001, 7(2), pages 203-210.) *teaches the general use of chitosan and/or collagen as biocompatible matrices for cell cultures/tissue constructs, including the culturing of human hemopoietic K62 cells.*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON J. KOSAR whose telephone number is (571)270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Aaron Kosar
Examiner, Art Unit 1651

/Sandra Saucier/
Primary Examiner, Art Unit 1651